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Absence of Hyperactivity in Lead-Exposed Developing Rats

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It has been reported that postnatal lead treatment produces hyperactivity in rodents. Using rats, we attempted to extend these findings. Locomotor activity of offspring of lead-intubated and pair-fed control mothers was measured at 24-27 days of age, and no significant differences in reactivity or basal activity were found. Observational scoring of the animals at 28-29 and 35-36 days of age indicated that active behaviors were slightly reduced in the lead-treated rats. The brain lead concentrations of experimental animals were significantly elevated over controls. Estimates of statistical power indicated that behavioral effects of the magnitude reported in the literature would likely have been detected. The present results indicate that low-level lead exposure may not reliably produce hyperactivity in rodents. A review of the literature suggests that other data provide little support for a recently proposed rodent model of hyperactivity in children.

Several behavioral effects of lead poisoning have been documented in the past several decades and include motor incoordination, reduced attention span, hyperactivity, irritability, and aggressiveness (*1-4*). More recently, it has been proposed that lead exposure at levels too low to cause gross symptoms might still produce behavioral problems (*5,6*). This proposal has been supported by some studies of children with low-level lead exposure (*7,8*) and opposed by others (*9*). Impairment of fine motor coordination (*7,8*), perceptual disorders (*8*), extreme negativism, distractability, and constant need for attention (*7*) are among the symptoms reported for these children.

It is also possible that some recognized behavioral disorders of unknown causation are due to low-level lead exposure. Thus, it has been suggested that some cases of the hyperactivity syndrome may have this etiology (*10*). This suggestion is attractive because a number of symptoms of hyperactivity in children (*11,12*) appear to be similar to those associated with lead poisoning (*1-4*). There is empirical support for this hypothesis in the findings (*13*) that hyperactive children with no known cause for the syndrome showed higher levels of lead in blood and urine (the latter following a chelator challenge) than did controls. Other children for which a highly probable cause of hyperactivity other than lead had been identified did not differ in lead levels from controls. This last result suggested that the elevated lead levels in the former hyperactive children were not caused by an increased ingestion of lead due to the hyperactivity. The elevated postchelator urine levels of lead in the hyperactive children indicated that they may have had increased body lead stores for a long time.

This interest in the behavioral effects of low-levels lead exposure in children has prompted studies of potential animal models for these ef-

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fects. Low-level lead exposure from birth onward has recently been reported to produce hyperactivity in rats (*14-17*) and mice (*18,19*), and the mice were further shown to display paradoxical drug effects similar to those in hyperactive children. The stimulant drugs *d*-amphetamine and methylphenidate reduced the activity of the lead-treated mice at doses which elevated activity in controls, while a depressant drug, phenobarbital, had the opposite pattern of effects. This "paradoxical" response to drugs is well known in hyperactive children (*20-22*) and, in fact, has been proposed as a major unifying feature of this rather diverse class of behavior problems (*22*). Thus, it has been suggested that this lead-induced behavioral change in rodents may serve as a model of hyperactivity in children (*19*).

There are, however, a number of methodological problems with the rodent studies which weaken these data. For instance, a substantially lower body weight was noted in hyperactive lead-treated mice (*18*). The mice were dosed as pups by the administration of lead through the mothers' water supply. If this reduced the water intake and milk production of the mothers, as is likely, the pups may have been subjected to undernutrition, which itself reliably produces hyperactivity (*23*). This possible confounding of lead and nutritional effects was avoided in the rat studies either by measuring the amount of lead-treated food the experimental mothers ingested and feeding equal quantities to the controls (*15-17*) or by administering lead directly to the pups (*14*). However, in the rat work, the reliability of the hyperactivity remains in question. No statistical analyses, measures of variability or sample sizes have been reported (*14-17*), and Sobotka and Cook (*24*) have recently failed to confirm the finding of hyperactivity in rats. The latter investigators still feel that the lead-treated rat may be a model for the hyperactive child since they found an altered responsiveness to a high dose of amphetamine. However, the drug did not actually reduce the activity of lead-treated animals, but rather increased it to a lesser extent than that of controls.

There are also some complications with the measurement of an animal's activity (*25,26*) which have received little attention in any of these rodent studies. For instance, activity measurements are influenced considerably by environmental stimuli, but it is not made clear in these studies to what degree this variable is controlled. Further, there is an important distinction to be made between basal activity and reactivity to stimulus change (*26*), and which of these two processes predominates depends greatly on the length of the time period during which activity is measured. Some of the lead studies used short periods (*18,19,24*) and have probably measured primarily reactivity, while others utilized a 24-hr period which would yield a measure reflecting mainly basal activity (*15-17*).

In addition, it is widely accepted that activity is not a unitary variable but rather a composite of many behaviors (*25,26*). This view is based on the fact that different measures of activity are often poorly correlated with each other both in animals (*27-31*) and in children (*32-34*). It is likely that different measures sample these behaviors in different proportions.

These complications make it doubtful that a single measure of reactivity or basal activity is adequate to establish a similarity between the behavior of lead-treated animals and that of hyperactive children. This view is also supported by the fact that the behavior of hyperactive children is believed to differ qualitatively from that of normal children, not simply to occur at a more rapid rate (*22,35,36*).

In studing lead-induced hyperactivity in rats, the present research has addressed certain of the above problems which have complicated previous rodent research. First, lead-treated and control mothers were pair-fed in an attempt to equate the nutritional status of the pups. Second, the activity measures were designed to assess both activity and reactivity measures, using specified environmental conditions and automated measures of activity. Third, direct observational scoring was also employed to obtain (1) a different measure of activity of lead-treated animals, (2) a more complete behavioral profile of lead-treated animals which could aid in assessing their potential as a model for behavior disorders in children, and (3) systematic data which might confirm previous observations of heightened self-grooming in lead-treated animals (*15-17*). Finally, to determine whether the lead had reached the brain, where it may exert its behavioral effects, the lead concentration in whole brain of some animals from each group was measured.

Methods

Subjects

Twenty-two 17-day pregnant female rats were obtained from the ARS Sprague-Dawley Com-

pany, Madison, Wisconsin. Each pregnant animal was housed in a plastic breeding cage (30 × 35 × 16.5 cm) and water was provided *ad libitum*. Entire litters were housed in these same cages for the duration of the experiment. The lighting cycle was 12 hr light (beginning at 7:30 A.M.) and 12 hr dark.

Apparatus

For the activity measurements, a photoactivity cage (BRS/LVE Model 145-03) in a lighted soundproof chamber was used. A transparent breeding cage (described above) was placed inside the photo-activity cage to make the test environment similar to the home cage (*17,18*). Two photocell beams crossed the long axis of the breeding cage, and one beam bisected its short axis. The first two beams were 13.5 cm apart and approximately 11 cm from the ends of the cage. Activity counts were the sum of all interruptions of these three beams. The beams did not pass under the animal's body and detect leg rather than whole body movements.

Direct observations were recorded with a set of clocks and counters controlled by a hand-held keyboard. One key was designated for each behavioral category, and the associated clock and counter recorded cumulative duration and frequency respectively for that behavior.

Procedure

To enable comparison of the present experiments with those of Michaelson and Sauerhoff (*15-17*) it was planned to replicate their method of administering the lead. However, in pilot work with four animals replication did not succeed. All animals refused food containing 5% lead acetate, $Pb(C_2H_3O_2)_2 \cdot 3H_2O$, almost entirely for 4-5 days, leading to severe emaciation and near death of both mother and pups. When the mother began to eat the diet, they rarely increased their consumption above 30 g/day, about 20 g/day less than previously reported (*15*) for the same strain of rat and an apparently identical diet.

Therefore, lead acetate was administered by intubation of the mothers, using a Robinson size 8 catheter coupled to a syringe. An attempt was made with additional pilot animals to determine the highest dose which would be tolerated by mothers after parturition. Administration of 1.67 g or more of lead acetate/kg body weight per day resulted within a few days in severe overt symptoms of lead poisoning in the mother followed by death of the pups.

The following lead treatment groups were, therefore, used: (1) low-lead group (LL) (six mothers): 0.83 g lead acetate/kg body weight/day beginning 2 days after parturition and continuing until weaning of the pups; (2) low-lead control (LLC) (six mothers): each mother was paired for feeding purposes to one mother in group LL and intubated with a similar volume of distilled water; (3) high-lead group (HL) (five mothers): identical to group LL except that dose was increased to 1.25 g/kg-day on day 9 after parturition; (4) high-lead control (HLC) (five mothers): paired to group HL exactly as group LLC was to group LL. The daily dose of lead acetate was divided equally between two intubations—one in the morning and the second about 12 hr later.

Litters were reduced to ten animals immediately after parturition and to six animals on day 5 (*17*). Equal numbers of males and females were kept in each litter whenever possible, and paired litters (i.e., offspring of pair-fed mothers, one lead-treated and one control) always had identical sex ratios. Thus, groups HL and HLC had the same number of animals of each sex, as did groups LL and LLC. One litter in each of groups LL and LLC had five pups rather than six, due to the death of a pup.

Mothers and pups were weighed daily at about 10:00 A.M. All litters were weaned on day 21 except for two pairs in the LL and LLC groups for which weaning was delayed until day 23 because of somewhat lower body weights of the pups.

Two animals from each litter, one male and one female, were sacrificed by decapitation on day 29 of life, and their brains were removed, wrapped in aluminum foil, and frozen for subsequent analysis of lead content.

Feeding

Pregnant animals were received in groups of four from the supplier. The first two of these to deliver their pups were always assigned to group LL or HL, and food was made available to them *ad libitum* throughout lactation. Each of the last two animals to deliver was paired to one of the first two (i.e. was assigned to group LLC or HLC) and was always offered only as much food as was eaten by the experimental animal on the previous day. The animals were fed following weighing each morning with Purina Lab Chow Meal placed in a cup fixed to a pan to catch spilled food. The

uneaten food remaining from the previous day was sifted free of litter and feces and weighed. On day 16 group LL was shifted to a diet containing 25 ppm lead as lead acetate (*15*) and group HL to a diet of 37.5 ppm lead. These diets, given to avoid reduction of lead intake by the pups when they began eating solid food, did not appreciably increase the total amount of lead received by the mothers (less than 1% increase for an animal consuming 50 g of food daily). The pups were maintained on their respective lead-containing diets after weaning, and entire litters were pair-fed as the mothers had been previously (except during activity testing).

Activity Measurement

Entire litters of animals, age 24-27 days, were transferred to the photoactivity apparatus 30 min before the beginning of the dark portion of the lighting cycle. Each litter was tested for a total of 23.5 hr. Water and the appropriate diets were provided *ad libitum*. The test cage was washed before testing of each litter.

Cumulative activity counts for the initial 30-min period constituted the measure of reactivity. Cumulative counts were also recorded 6 hr after the beginning of the dark period and at the end of the 12-hr dark period. The chamber light was then turned on and activity was again recorded 6 and 11 hr later, at which time the animals were returned to their home cages.

Litters of a pair were always tested at the same age except for those born on the same day where order of testing was counterbalanced.

Note that the effective unit of observation for these measures was litter, rather than individual subject (*17*). Thus, here $n = 6$ for groups LL and LLC and $n = 5$ for HL and HLC.

Direct Observation

Individual animals were removed from their home cages on day 28 or 29 of life and again on day 35 or 36, placed in a breeding cage in a lighted soundproof chamber, and observed for 10 min through a window in the chamber. Animals from litters of a pair were always observed at the same age and at about the same time of day. Observation was done in the last half of the light period.

Three animals were randomly selected from each litter for observation but the sex ratios for paired litters were kept identical, and approximately equal numbers of males and females were observed in each group. The same animals were observed for the two observation periods. The cage was cleaned before observation of each animal.

One pair of litters in the LL and LLC groups had to be excluded because of development of obvious respiratory illness at about 30 days of age. A pair of litters from the HL and HLC groups was also excluded because they were briefly given the wrong diet at this age. As a result $n = 5 \times 3 = 15$ for LL and LLC groups, and $n = 4 \times 3 = 12$ for HL and HLC groups. Behavior was classified according to the following categories: locomotion, rearing, self-grooming, exploratory sniffing (*37*) and inactivity. Sniffing could occur at the same time as the first two categories, but all other categories were mutually exclusive. Inactivity was scored whenever all active behaviors were absent. This category included freezing as well as short bouts of inactivity when the animal was obviously alert. Two other categories, chewing and climbing, were defined but occurred so infrequently that the data could not be analyzed.

Determination of Brain Lead Concentration

Lead concentrations of whole brain were determined by atomic absorption spectrophotometry. Brain tissue was prepared using nitric acid-washed glassware. After determination of brain dry weights, 2 ml of concentrated HNO_3 (Aristar HNO_3, lead content < 0.001 ppm, BDH Chemicals Ltd.) was added to each brain. Samples were covered and digested at room temperature for 24 hr, then boiled down to 0.5 to 1 ml. This digest was diluted to 10 ml with double-distilled water. The lead concentrations of a 10 µl sample of this solution was determined by using a Perkin-Elmer model 503 atomic absorption spectrophotometer (dual beam) with a heated graphite atomizer (HGA-2100).

The two control groups were combined for the purposes of the statistical analysis since their lead exposure should have been the same.

Results

Activity

The 23-hr activity patterns for lead-treated and pair-fed control litters are shown in Figure 1. A two-way analysis of variance with lead treatment as a between-subjects variable was performed on the data for each lead-treatment group together with its pair-fed control group. In both instances there was no significant main effect of lead (LL and LLC: $F < 1$; HL and HLC: $F < 1$). While ac-

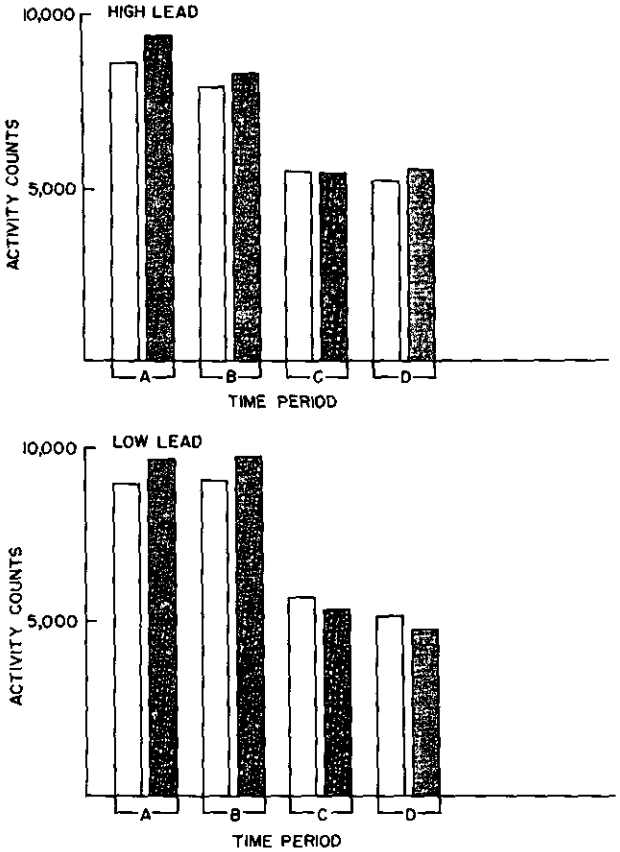

FIGURE 1. Activity patterns (23 hr) of lead-treated and control litters for (upper panel) groups HL and HLC and (lower panel) groups LL and LLC: (*A*) first 6 hr of dark portion of lighting cycle; (*B*) last 6 hr of dark portion; (*C*) first 6 hr of light portion; (*D*) hours 7 to 11 of light portion. Light bars: lead-treated animals; dark bars: control animals.

tivity did change significantly during the test period (LL and LLC: $F = 83.69$, df = 3/30, $p < 0.001$; HL and HLC: $F = 40.41$, df = 3/24, $p < 0.001$), the patterns of activity change did not differ for lead-treated and control animals (LL and LLC: $F = 1.467$, df = 3/30, $p > 0.2$; HL and HLC: $F < 1$).

Since there were previous reports of a 40% or greater elevation in activity of lead-treated litters on a similar measure (*17*), power calculations were made with α set at 0.05 (*38*) and indicated a power of at least 0.90, that is, a 90% chance that the present study would have detected an effect of that magnitude.

Reactivity

Neither lead dosage group differed significantly (Student's t) from its respective pair-fed control group in activity for the first thirty minutes in the photocell apparatus (Table 1). A power calculation for an effect of lead treatment of at least 40% of the mean of the combined control groups at $\alpha = 0.05$ revealed a 97% chance of detection in this study (*39*).

Table 1. Mean activity counts during the first half-hour in the photoactivity cage for lead-treated and control litters.

Dose	Activity ± S.D.	
	Lead group	Pair-fed control
Low	1453 ± 193	1431 ± 231
High	1333 ± 226	1482 ± 184

Direct Observation

The mean frequency and duration of each behavior averaged across sexes and the two ages at testing are shown in Figure 2.

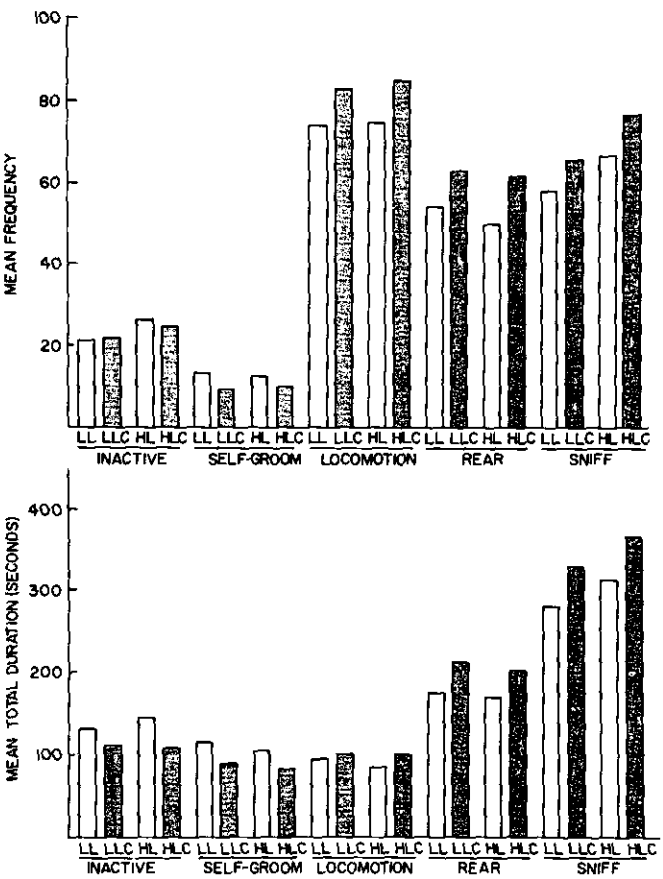

FIGURE 2. Direct observation: Mean frequencies and durations per 10-min session of each behavior for each treatment group: light bars: lead-treated animals; dark bars: control animals. Scores were averaged across sex and age at testing.

A separate analysis of variance was performed on the frequency data and on the duration data for each of the five behaviors with lead treatment and sex as completely crossed between-subjects factors and age at testing as a within-subjects factor. The behaviors for which there was at least a marginally significant main effect of lead treatment or interaction of lead treatment with some other factor are shown in Table 2. No striking effects of lead were observed in either group. In all, 60 F-tests for main effects of lead and for one-way interactions of lead treatment with other factors were performed. Thus the number which attained statistical significance for $\alpha = 0.05$ was only slightly more than expected by chance. However, the direction of differences between lead-treated and control animals was the same for high-lead and low-lead groups in all instances except frequency of inactive periods, where differences were comparatively small. All active behaviors except self-grooming occurred with lower frequency and shorter duration in lead-treated animals. The slight reduction in active behaviors is in accord with the slight reduction in reactivity of the high lead group as measured by the photocell apparatus.

The absence of statistically reliable effects appears to have been due to the fact that any effects of lead were small rather than to excessive variability. The estimated powers to detect a change in these measures equal to 40% of the control mean were calculated as for the activity scores (*38*). Power estimates for frequency and duration of locomotion, rearing, and sniffing ranged from 0.59 to greater than 0.99, with most estimates greater than 0.80. Power estimates for inactivity and self-groom were somewhat lower but still substantial. Furthermore, all these estimates were probably conservative since there would be positive bias in the F-tests for main effects of lead treatment if there was any significant variance due to litter (*40*).

Brain Lead

Mean concentrations (μg/g dry weight ± standard deviations) of lead in brain tissue of 29-day old animals were as follows: 2.00 ± 0.03 (HLC), 1.70 ± 0.19 (LLC) and 1.05 ± 0.09 (controls). Planned comparisons of these means (39) revealed that the low lead group ($n = 6$) differed significantly from the control group ($n = 11$) ($F = 50.68$, df = 1/19, $p < 0.001$) and that the high-lead ($n = 5$) and low-lead groups were significantly different from each other ($F = 7.64$, df = 1/19, $p < 0.025$).

Food Consumption and Body Weight of Mothers

The food consumption of the mothers was considerably lower early in lactation than that reported by Michaelson and Sauerhoff (*15*), but it gradually reached a similar level by day 17. Some animals showed a much more severe depression of eating than others, especially during the first few days of lead treatment. Although control and lead-treated animals ate the same amount of food because of the paired-feeding, the pattern of feeding during the day appeared quite different for the two groups. Control animals generally ate most or all of their food immediately after the morning feeding, whereas lead-treated animals, having food available *ad libitum*, fed throughout the day.

The patterns of weight change differed slightly between lead-treated and control mothers (lead treatment × time interaction, HL and HLC: $F = 4.63$, df = 21/168, $p < 0.001$; LL and LLC: $F = 3.27$, df = 21/209, $p < 0.001$). The weight of the

Table 2. Main effects of lead treatment and lead-treatment interactions attaining significance at α=0.10.

Behavioral Category	Groups	Source of Variance	F	df	p
Locomotion duration	HL and HLC	lead	3.33	1 and 20	<0.10
Rearing frequency	HL and HLC	lead	4.95	1 and 20	<0.05
Sniffing duration	HL and HLC	lead	12.77	1 and 20	<0.005
Self-groom frequency	LL and LLC	lead	6.38	1 and 26	<0.025
Inactivity duration	LL and LLC	lead × sex	4.44	1 and 26	<0.05
Inactivity frequency	LL and LLC	lead × age	3.40	1 and 26	<0.10

lead-treated mothers returned to its initial level by the end of lactation, while that of controls did not (Fig. 3).

Body Weights: Pups

Mean body weights for pups through day 24 of life are presented in Figure 4. There were no significant differences in body weight between lead-treated and control groups. However, litters within treatment conditions differed significantly from one another in mean body weight (HL and HLC: $F = 74.5$, df = 8/50, $p < 0.001$; LL and LLC: $F = 108.0$, df = 10/58, $p < 0.001$) and in pattern of weight gain over time (litter × time/treatment condition, HL and HLC: $F = 13.09$, df = 192/1200, $p < 0.001$; LL and LLC: $F = 27.13$, df = 230/1334, $p < 0.001$).

Discussion

The present behavioral data are not in accord with the reports of Michaelson et al. (*14-17*) and Silbergeld and Goldberg (*18,19*). Almost no statistically significant effects of lead on any of the behavioral meansures were found, even though estimates of power indicated that effects of the magnitude previously reported would likely have been detected for most of the present measures. In fact, the present data suggest slight decreases, rather than increases, in frequency and duration of all active behaviors except self-grooming, at least over a short test period. The absence of a significant effect of lead upon reactivity as assessed by the first one-half hour in the photoactivity cage concurs with the findings of Sobotka and Cook (*24*) for a 15 min measurement in a similar apparatus. Previous reports of heightened self-grooming in lead-treated animals (*15-17*) receive some confirmation from the present study.

It is worth considering the possibility that any subtle differences in behavior between lead-treated and control pups may have been produced by the differing feeding patterns (see Results) and reactivity of the mothers. Control mothers always appeared much more reactive to handling and to stimuli around their cages than did lead-treated mothers, presumably because of the partial food deprivation of the controls (*41*). That the mothers' behavior could be an important factor is suggested also by its demonstrated role in producing the behavioral effects of an infant malnutrition paradigm (*23*).

Species differences might account for the differences between the present results and those of

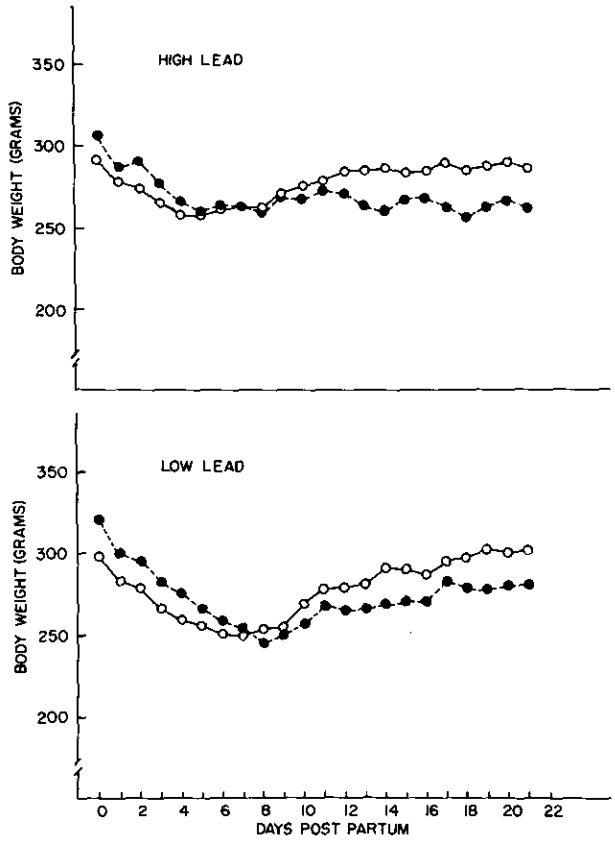

FIGURE 3. Mean body weights of mothers from parturition through weaning of the pups of (upper panel) groups HL and HLC and (lower panel) groups LL and LLC: (○) lead groups; (●) controls.

Silbergeld and Goldberg (*18*), although nutritional deprivation (discussed in the Introduction) could also account for the hyperactivity observed in their lead-treated mice. The paired-feeding procedure employed in the present study seems to have prevented this possible confounding of the effects of lead and nutrition, since lead-treated and control pups were not significantly different in body weight. The presence of significant differences in body weight between litters in the present study is probably related to the differences in food intake between mothers. These litter differences further underline the importance of paired-feeding in controlling nutritional factors.

It is difficult to explain why hyperactivity was not found in the present study as it was in those of Michaelson et al. (*14-17*), although the latter data are difficult to evaluate because of their lack of statistical analysis. It is possible, although it seems unlikely, that different types of activity

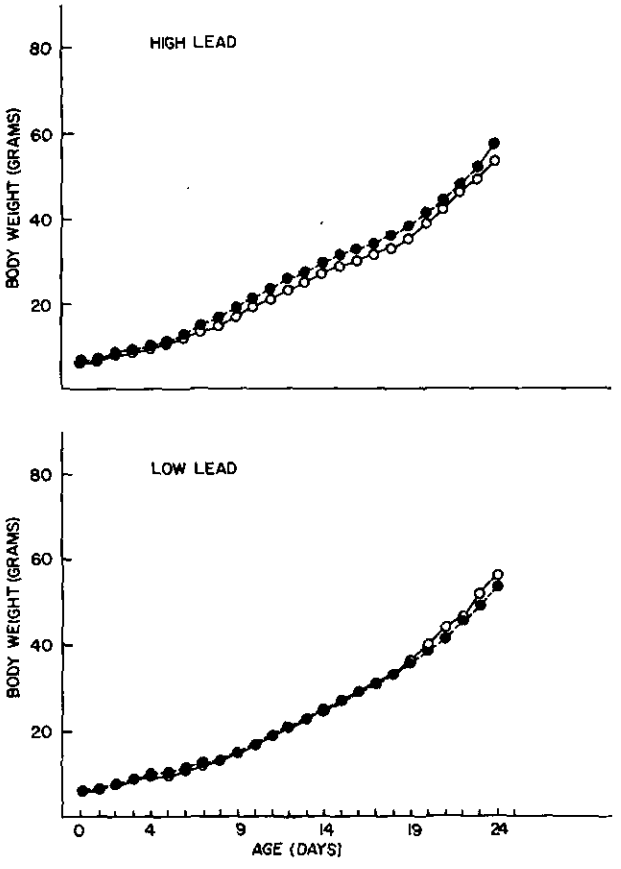

FIGURE 4. *Mean body weights of pups from birth until activity testing was done for (upper panel) groups HL and HLC and (lower panel) groups LL and LLC: (○) lead-treated animals; (●) controls.*

were measured in the two studies since different apparatus were used (*25*). Recent unpublished studies in other laboratories have also failed to find increased activity in lead-treated rats (L. Grant, personal communication). In addition, the present study and that of Sobotka and Cook (*24*) found no change in reactivity as well.

Possible differences in lead dose between the present study and those of Michaelson et al. (*14-17*) might also be relevant, but are difficult to evaluate since the dose given the pups was not measured directly in these studies and since there is no systematic dose-response information available. The amount of lead acetate administered to the mothers via the food by Michaelson and Sauerhoff (mean of 1.85 g/day) (*15*) was clearly greater than that administered by intubation in the present study (350-400 mg/day in the HL group). It is likely, however, that a greater percentage of the lead is absorbed from water than from food (*42*). In a pilot study we were unable to administer lead in the manner described by Michaelson and Sauerhoff (*15*) without a more severe self-starvation of lead-treated animals than they report.

The doses given the mothers in the present study appear to be near the maximum tolerable level. A lower dose of lead acetate (about 55% of that for the LL group) was found to be lethal in 19 of 30 nonlactating rats intubated daily for 50 days (*43*). If the mothers in the present study are assumed to have absorbed 2.61% of the orally administered lead (*44*), than they absorbed daily the lead contained in 21.7 mg of lead acetate, almost twice the LD_{33} for 37 days of intraperitoneal injections (*45*).

Brain lead concentrations for the HL group of the present study (2.00 μg/g dry weight) were similar to those reported by Michaelson and Sauerhoff (*15*) for animals showing hyperactivity (about 2.27 μg/g dry weight assuming the brain is 78% water). The control values were higher in the present experiment (1.05 μg/g) than in that of Michaelson and Sauerhoff (*15*) (about 0.45 μg/g), but are nearer to those in another study (about 0.73 μg/g) in which hyperactivity of lead-treated animals was also found (*14*). Even higher brain lead concentrations for control animals have been found in brains of 45-day old rats (about 2.7 μg/g) (*46*) and of 6-month old rats (about 1.27 μg/g) (*47*).

Thus, although it is uncertain that the animals in the present study received exactly the same dose of lead as did the hyperactive animals in previous studies, it is clear that they received a very substantial dose and one in the general range used in the other studies. The difference between the present behavioral effects of lead and those found in previous studies suggests at the very least that the relationship between lead dosage and locomotor activity may not be a simple one—perhaps different doses result in opposite effects. Another possibility is that differing patterns of dosage during development result in quite different effects.

A compelling interest in lead-induced hyperactivity in rodents stems from Silbergeld and Goldberg's (*19*) proposal that this syndrome could serve as a model for some forms of hyperkinesis in children. They were encouraged in this proposal by the finding that the rodent hyperactivity responded "paradoxically" to amphetamine (sedation) and to phenobarbital (exacerbation). However, it can be questioned whether the "paradoxical" response to amphetamine is unique either to lead-treated animals or to hyperactive

children. Fish (*48*) concluded that the effectiveness of amphetamine for treating behavioral disorders of children was not dependent on the presence of hyperactivity, but rather acted to improve disorders characterized as overanxious or unsocialized aggressive reactions. Further, it is uncertain whether the response of hyperactive children to amphetamine is truly paradoxical, since the response of normal children to amphetamine has not been investigated (*49*). In fact, a large proportion of normal human adults have been shown to exhibit paradoxical sedative responses to amphetamine (*50*).

Similarly, there are a number of animal studies suggesting that the paradoxical sedative action of amphetamine is not paradoxical at all but rather is the normal characteristic of individuals that are hyperkinetic for whatever cause. Rodents with a predrug activity level at the high end of a normal continuum, for instance, are depressed by a dose of amphetamine which elevates activity in those at the low end of the continuum (*51,52*). A similar paradoxical effect is seen in animals whose basal activity has been raised by brain damage (*53*). Sufficiently high doses of amphetamine are a sedative for all animals (*52*), and an increased sensitivity of hyperkinetic animals to amphetamine may explain some of these results.

Recent studies of children with an elevated body lead burden have also failed to establish a link between lead exposure and hyperactivity. Lansdown and associates found no significant relationship between blood lead levels and several behavioral measures including activity (*9*). The latter study may have underestimated the incidence of hyperactivity in several ways (*54*). For example, the behavior rating scale used was not designed specifically to detect hyperactivity. However, in another study in which such a scale was used (*8*), no elevation in incidence of hyperactivity was found in children with high blood lead levels. In a third investigation seven of twenty-one children with evidence of high body lead burdens were reported to be hyperactive, but no information was given as to how activity was assessed (*55*).

The present results do not constitute evidence that low levels of lead have no behavioral-teratological effects. The post-parturitional exposure employed in the present study and in others reviewed here misses completely the teratologically vulnerable period of gestational organogenesis (about day 10 of gestation in the rat) (*56*). In addition, probably very little lead is absorbed by the pups by day 3 of life when the most rapid cell division is occurring in the brain. This age is posited to be a very vulnerable one for neurological (and, hence, behavioral) teratology (*57*). While the data reviewed here raise considerable doubt that post-parturitional exposure to low levels of lead produces hyperactivity in rodents or in children, it is still possible that a certain tissue lead level must be attained during a restricted critical developmental period in order to produce such a teratological effect. This possibility has not yet been investigated.

In conclusion, the present results, as well as other recent studies, call into question whether a link between lead and hyperactivity can be reliably demonstrated, either in rodents or in children. Even if lead dosage parameters can be identified for reliably inducing hyperactivity, much additional work would be required to demonstrate the qualitative similarity of rodent and human hyperkinesis. Demonstrations of paradoxical amphetamine effects do little to strengthen the analogy, since they may occur for any hyperkinesis regardless of cause. Thus, the data presently available provide little support for the proposal of lead-induced hyperactivity in rodents as a model for hyperactivity in children.

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REFERENCES

1. Byers, R. K., and Lord, E. E. Late effects of lead poisoning on mental development. Am. J. Dis. Child. 66: 471 (9143).
2. Chisolm, J. J., Jr. Lead poisoning. Sci. Am. 224(2): 15 (1971).
3. Cohen, G. J., and Ahrens, W. E. Chronic lead poisoning. J. Pediatr. 54:271 (1959).
4. National Academy of Seciences. Lead: Airborne Lead in Perspective. Washington, D. C., 1972.
5. Weiner, G. Varying psychological sequelae of lead ingestion in children. Public Health Repts. 85(1): 19 (1970).
6. Chisolm, J. J., Jr. Chronic lead intoxication in children. Dev. Med. Child. Neurol. 7: 529 (1965).
7. de la Burde, B., and CHoate, M. S., Jr. Does asymptomatic lead exposure in children have latent sequelae? J. Pediatr. 81: 1088 (1972).

8. Whitworth, R. H., et al. Follow-up on human lead absorption—Texas. Morbidity Mortality Weekly Rept. 23(18): 157 (1974).
9. Lansdown, R. G., et al. Blood-lead levels, behavior, and intelligence: a population study. Lancet, (I): 538 (1974).
10. David, O. J. Association between lower level lead concentrations and hyperactivity in children. Environ. Health Perspect. 7: 17 (1974).
11. Laufer, M. W., and Denhoff, E. Hyperkinetic behavior syndrome in children. J. Pediatr. 50: 463 (1957).
12. Laufer, M. W., Denhoff, E., and Solomons, G. Hyperkinetic impulse disorder in children's behavior problems. Psychosom. Med. 19(1): 38 (1957).
13. David, O., Clark, J., and Voeller, K. Lead and hyperactivity. Lancet (II): 900 (1972).
14. Golter, M., and Michaelson, I. A. Growth, behavior and brain catecholamines in lead-exposed neonatal rats: A reappraisal. Science 187: 359 (1975).
15. Michaelson, I. A., and Sauerhoff, M. W. An improved model of lead-induced brain dysfunction in the suckling rat. Toxicol. Appl. Pharmacol. 28: 88 (1974).
16. Michaelson, I. A., and Sauerhoff, M. W. Animal models of human disease: Severe and mild lead encephalopathy in the neonatal rat. Environ. Health Perspect. 7: 201 (1974).
17. Sauerhoff, M. W., and Michaelson, I. A. Hyperactivity and brain catecholamines in lead-exposed developing rats. Science 182: 1022 (1973).
18. Silbergeld, E. K., and Goldberg, A. M. A lead-induced behavioral disorder. Life Sci. 13: 1275 (1973).
19. Silbergeld, E. K., and Goldberg, A. M. Lead-induced behavioral dysfunction: an animal model of hyperactivity. Exp. Neurol. 42: 146 (1974).
20. Millichap, J. G. Drugs in management of minimal brain dysfunction. Ann. N.Y. Acad. Sci. 205: 321 (1973).
21. Sykes, D. H., et al. Attention in hyperactive children and the effect of methylphenidate (Ritalin). J. Child Psychol. Psychiatry. 12: 129 (1971).
22. Wender, P. H. Minimal Brain Dysfunction in Children. Wiley-Interscience. New York, 1971.
23. Slob, A. K., Snow, C. E., and de Natris-Mathot, E. Absence of behaviroal deficits following neonatal undernutrition in the rat. Dev. Psychobiol. 6: 177 (1973).
24. Sobotka, T. J., and Cook, M. P. Postnatal lead acetate exposure in rats: Possible relationship to minimal brain dysfunction. Am. J. Ment. Defic. 79: 5 (1974).
25. Baumeister, A., Hawkins, W. F., and Cromwell, R. L. Need states and activity level. Psychol. Bull. 61: 438 (1964).
26. Gross, C. G. General activity. In: Analysis of Behavioral Change. L. Weiskrantz, Ed., Harper and Row, New York, 1968.
27. Finger, F. W. Estrous activity as a function of measuring device. J. Comp. Physiol. Psychol. 54: 524 (1961).
28. Finger, F. W. Estrus and general activity in the rat. J. Comp. Physiol. Psychol. 68: 461 (1969).
29. Strong, P. N., Jr. Activity in the white rat as a function of apparatus and hunger. J. Comp. Physiol. Psychol. 50: 596 (1957).
30. Treichler, F. R., and Hall, J. F. The relationship between deprivation weight loss and several measures of activity. J. Comp. Physiol. Psychol. 55: 346 (1962).
31. Weasner, M. H., Finger, F. W., and Reid, L. S. Activity changes under food deprivation as a function of recording device. J. Comp. Physiol. Psychol. 53: 470 (1960).
32. Cromwell, R. L., Baumeister, A., and Hawkins, W. F. Research in activity level. In: Handbook of Mental Deficiency. N. R. Ellis, Ed., McGraw-Hill, New York 1963.
33. McConnell, T. R. et al. Studies in activity level: VII. Effects of amphetamine drug administration on the activity level. Am. J. Ment. Defic. 68: 647 (1964).
34. Shaffer, D., McNamara, N., and Pincus, J. H. Controlled observations on patterns of activity, attention, and impulsivity in brain-damaged and psychiatrically disturbed boys. Psychol. Med. 4: 4 (1974).
35. Freedman, D. X. Report of the conference on the use of stimulant drugs in the treatment of behaviorally disturbed young school children. Psychopharmacol. Bull. 7: 23 (1971).
36. Werry, J. S., and Sprague, R. L. Hyperactivity. In: Symptoms of Psychopathology, a Handbook. C. G. Costello, Ed., Wiley, New York, 1970.
37. Campbell, B. A., and Mabry, P. D. Ontogeny of behavioral arousal: A comparative study. J. Comp. Physiol. Psychol. 81: 371 (1972).
38. Myers, J. L. Fundamentals of Experimental Design. Allyn and Bacon, Boston, 1972, p. 89.
39. Hays, W. L. Statistics for the Social Sciences. Holt, Rinehart and Winston, New York, 1973, pp.411, 584.
40. Albey, H., and Howard, E. Statistical procedure in developmental studies on species with multiple offspring. Dev. Psychobiol. 6: 329 (1973).
41. Campbell, B. A., and Sheffield, F. D. Relation of random activity to food deprivation. J. Comp. Physiol. Psychol. 46: 320 (1953).
42. Karhausen, L. Intestinal lead absorption. In: Proceedings of the International Symposium on the Environmental Health Aspects of Lead. Commission of the European Communities, Luxembourg, 1973.
43. Diaz-Rivera, R. S., and Horn, R. C., Jr. Postmortem studies on hypertensive rats, chronically intoxicated with lead acetate. Proc. Soc. Exptl. Biol. Med. 59: 161 (1945).
44. Kostial, K., and Momcilovic, B. The effect of lactation on the absorption of ^{203}Pb and ^{47}Ca in rats. Health Phys. 23: 383 (1972).
45. Snowdon, C. T. Learning deficits in lead-injected rats. Pharmacol. Biochem. Behav. 1: 599 (1973).
46. Fjerdingstad, E. J., Danscher, G. and Fjerdingstad, E. Hippocampus: Selective concentration of lead in the normal rat brain. Brain Res. 80, 350 (1974).
47. Krigman, M. R., et al. Subcellular distribution of lead in the brains of intoxicated and control rats. J. Neuropathol. Exp. Neurol. 33: 562 (1974).
48. Fish, B. The "one child, one drug" myth of stimulants in hyperkinesis. Arch. Gen. Psychiatry. 25: 193 (1971).
49. Eisenberg, L. The clinical use of stimulant drugs in children. Pediatrics. 49, 709 (1972).
50. Tecce, J. J., and Cole, J. C. Amphetamine effects on man: Paradoxical drowsiness and lowered electrical brain activity (CNV). Science 185: 451 (1974).
51. Glick, S. D., and Milloy, S. Rate-dependent effects of d-amphetamine on locomotor activity in mice: Possible relationship to paradoxical amphetamine sedation in minimal brain dysfunction. Eur. J. Pharmacol. 24: 266 (1973).
52. Heffner, T. G., Drawbaugh, R. B., and Zigmond, M. J. Amphetamine and operant behavior in rats: Relationship between drug effect and control response rate. J. Comp. Physiol. Psychol. 86: 1031 (1974).

53. Sechzer, J. A. et al. A possible animal model for minimal brain dysfunction. Anat. Rec. 178: 522 (1974).
54. David, O. J. Blood-levels, behaviour, and intelligence. Lancet (I): 866 (1974).
55. Roberts, T. M., et al. Lead contamination around secondary smelters: Estimation of disposal and accumulation by humans. Science 186: 1120 (1974).
56. Wilson, J. M. Introduction: Problems of teratogenic testing. In: Toxicity of Anesthetics. B. R. Fink, Ed., Williams and Wilkins, Baltimore, 1968.
57. Dobbing, J. Vulnerable periods in developing brain. In: Applied Neurochemistry. A. N. Davison and J. Dobbing, Eds., F. A. Davis Co., Philadelphia, 1968.